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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US00/02638 <b>(22) International Filing Date:</b> 2 February 2000 (02.02.00) <b>(30) Priority Data:</b> 09/243,289 2 February 1999 (02.02.99) US <b>(71) Applicant (for all designated States except US):</b> AVON PRODUCTS, INC. [US/US]; 1251 Avenue of the Americas, New York, NY 10020 (US). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> ANDERSON, Glen, T. [US/US]; 150 Locust Avenue, Cortlandt Manor, NY 10566 (US). <b>(74) Agent:</b> RUGGIERO, Charles, N., J.; Ohlandt, Greeley, Ruggiero & Perle, L.L.P., 9th floor, One Landmark Square, Stamford, CT 06901-2682 (US).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> METHODS FOR ALLEVIATING DISCOMFORT OF A HOT FLASH AND COMPOSITIONS THEREFOR  <b>(57) Abstract</b> <p>The present invention relates to a method of alleviating the discomfort, such as the feeling of intense heat, experienced by a woman during a hot flash. The present invention also relates to compositions that may be used to practice the foregoing method. More particularly, the present invention relates to the topical application of compositions having cooling compounds as a method of alleviating discomfort experienced by a woman during a hot flash.</p>		

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## METHODS FOR ALLEVIATING DISCOMFORT OF A HOT FLASH AND COMPOSITIONS THEREFOR

### BACKGROUND OF THE INVENTION

5       The present invention relates to a method of alleviating discomfort experienced by a woman during a hot flash. The present invention also relates to the method of use of topical compositions that may be used to alleviate such discomfort. More particularly, the present invention relates to a method of alleviating discomfort, especially the feeling of intense heat,  
10       experienced by a woman during a hot flash and the topical application of a composition having cooling ingredients in order to alleviate such discomfort.

#### 1. Field of the Invention

15       It is believed that a vast majority, perhaps as much as 80 percent, of women experience the discomfort of the "hot flash/flush" associated with menopause. A hot flash is believed to be the result of the hormonal changes, particularly the decline in estrogen levels, that occur during menopause. (Although some sources differentiate between a "hot flash"  
20       and "hot flush," both conditions will be referred to herein collectively as "hot flash" or "hot flashes.")

      A hot flash is marked by an increase in body temperature accompanied by an intense feeling of unbearable heat, particularly  
25       internally radiating body heat. A hot flash may also be accompanied by an increase in heart rate, dizziness, anxiety, faintness, a sense of unease, tingling sensations, pressure in the head, nausea, perspiration, and feelings of breathlessness. The feeling of heat is often concentrated in the area of the face and neck, and sometimes spreads to the area of the upper  
30       chest. Although a hot flash may last for as short as a minute, a hot flash usually lasts as long as two to three minutes, and may last as long as an hour. Regardless of the duration of the hot flash, the discomfort due to the

intense feeling of heat is extremely uncomfortable and disconcerting to a woman experiencing the hot flash.

## 2. Description of the Related Art

5 Perhaps the most common treatment of a hot flash is Hormone Replacement Therapy (HRT), more specifically Estrogen Replacement Therapy (ERT). Some sources recommend vitamin supplements, such as vitamin E and bioflavonoids, to treat a hot flash. These treatments are systemic methods of treatment that require foresight. In addition in the  
10 case of HRT/ERT, one needs a prescription from a medical professional.

U.S. Patent No. 5,730,957 to Rizk describes the use of a cooling composition having dimethyl ether and water to alleviate the discomfort associated with heat. This cooling composition utilizes the latent heat of  
15 vaporization to provide its cooling action and also requires that the cooling composition be at a temperature below ambient temperature and higher than the freezing point of water. This patent also provides a method of maintaining the cooling composition at such a temperature that requires a pressurized dispensing container. In addition, the sole embodiment  
20 described in the Rizk patent is a water-dimethyl ether composition contained within an aerosol dispenser (col. 3, line 51 et seq.). In addition to the fact that maintaining the composition at a cold temperature is an inconvenient and impractical requirement, the use of dimethyl ether has known safety issues.

25 Some prior art provides for topical cooling of the skin. For example, U.S. Patent No. 5,703,123 to Pelzer et al. describes the use of compositions having asymmetric carbonates, thiocarbonates and/or carbonates to create a physiologic cooling effect on the skin and on  
30 mucosae in compositions such as food stuffs (e.g. beverages, jams,), cosmetic agents (e.g. shaving products, skin care products, etc.), household products (e.g. fabric softeners) and pharmaceutical preparations

(e.g. antiseptic ointments, cough mixtures). U.S. Patent No. 5,266,692 to Grub et al. provides that ketals, such as 1-methone glycerol ketal or 3,3,5-trimethylcyclohexanone glycerol ketal, have a physiological cooling effect when applied to the skin or mucous membranes in preparations, such as dentifrices, mouth washes, perfumes and shaving foams. In addition, U.S. Patent No. 5,688,497 to Lozeau et al. discloses shaving aids that provide a physiological cooling effect.

U.S. Patent No. 5,451,404 to Furman, the disclosure of which is incorporated herein by reference, provides coolant compositions that may be administered topically. Also, U.S. Patent No. 4,661,476 to Lane et al. describes a method of cooling skin overheated by exposure to heat, sun or wind that is the topical application of an aqueous gel having a starch-polyacrylamide graft copolymer.

U.S. Patent No. 5,595,970 to Garfield et al. describes the use of a nitric oxide substrate and/or nitric acid donor, either alone or in combination with a progestin or estrogen to alleviate climacterium symptoms such as hot flashes. However, the compositions disclosed in Garfield et al. require systemic administration.

Until now, there has not been a method of alleviating the discomfort of hot flashes experienced by women that is non-systemic, easy to use and relatively inexpensive.

## SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method of alleviating the discomfort associated with a hot flash.

It is another object of the present invention to provide such a method for alleviating the feeling of intense heat associated with a hot flash.

It is a further object of the present invention to provide such a method that includes the topical application of a composition having a cooling agent.

5 The present invention, in brief summary, is a method of alleviating the discomfort associated with hot flashes that comprises the step of applying to the body, particularly to the chest, face and neck area and/or to the wrist and arm area, a topical cooling composition having at least one cooling agent.

## 10 DETAILED DESCRIPTION OF THE INVENTION

Hot flashes are most commonly associated with the discomforting symptom of an intense feeling of heat that begins in the face, neck, or chest regions and then radiates to other parts of the body. However, prior to the intense feeling of heat, many women experience a premonition of an  
15 impending hot flash that is accompanied by symptoms, such as a feeling of unease or anxiety, a feeling of pressure in the head, or tingling sensations. During this time, there is a concurrent increase in heart rate, digital blood flow, and vasodilation of blood vessels of the skin. At this point, women will experience an intense feeling of heat and which may further be  
20 accompanied by feelings of dizziness, nausea and breathlessness.

For most women who experience hot flashes, these foregoing symptoms are very unpleasant. Indeed, for some women the extent of these symptoms experienced during a hot flash can be downright  
25 unbearable.

The first detectable change is an increase in finger blood flow with a concomitant enhancement of skin conductance, as well as a change in temperature of the skin of the face and neck. The increase in skin  
30 conductance is followed rapidly by a sharp rise (1-7°C) in finger temperature. The degree to which finger temperature rises during a hot flash is inversely proportional to the base-line finger temperature before the

flash. Thus, a 0.5°C increase in finger temperature in a woman with a base-line finger temperature of 35°C may be as good a measure of the occurrence of a hot flash as a 5°C increase in finger temperature in a woman with base-line finger temperature of 29°C, because of the non-linear relationship between skin temperature and blood flow.

As vasodilation and sweating ensue, internal body temperature drops. The magnitude of decrease in core temperature ranges from 0.1°C to 0.9°C. The onset of sweating is rapid and is particularly profuse in the face and scalp. It may occur in five minute bursts accompanying short, discrete hot flashes, or continue in waves for more than thirty minutes during prolonged hot flashes.

A hot flash is the inverse of a fever. In mammals, the control of body temperature resembles a negative feedback system in which a set point temperature serves as reference for the thermoregulatory mechanism. A fever can be understood as the upward adjustment of this temperature set point. In a febrile episode, the set point is first elevated, initiating vasoconstriction, shivering and behavioral modifications, such as the addition of blankets. This results in an elevation of body temperature to a level that is maintained for a period of time. A hot flash, on the other hand, is a transient downward adjustment of the set point, which results in the sensation of heat. At the end of a hot flash, the set point returns to normal. The trigger for a change in set point may be a series of nerve impulses. A fever, even with a rapid onset, may last for hours, days or even weeks. In contrast, the duration of a hot flash is in the order of minutes.

The present invention provides a method of alleviating discomfort experienced by a woman during a hot flash that occurs during menopause including alleviating the feeling of intense heat. The present invention further provides a method of alleviating symptoms of physical discomfort resulting from increased heart rate and digital blood flow associated with



hot flashes. The method of the present invention includes the step of applying topically to the woman a cooling composition having at least one cooling agent.

5           Although to practice the method of the present invention, a woman experiencing a hot flash may apply the topical cooling composition to any part of her body that feels overheated, it is preferred that the cooling composition is applied topically to the head and/or neck areas. It is more preferred that the cooling composition is applied topically to the face and  
10 neck areas. It is most preferred that the cooling composition is applied topically to the temples.

          To practice the present invention, the cooling composition, which is considered a topical composition, may be a solution, gel, cream, lotion,  
15 emulsion, solid stick, towelette or spray. It is preferred that the topical cooling composition is a stick, spray or a towelette. However, the topical cooling composition may be any form that may be quickly and easily applied to the head and neck areas.

20           To practice the present invention, the topical composition must have at least one cooling agent. The cooling agent must be suitable for topical application. As stated above, U.S. Patent No. 5,730,957 to Rizk discloses a cooling mixture of water and dimethyl ether. The cooling agents of the present invention are not a mixture of dimethyl ether and water. In  
25 addition, the cooling mixture of the Rizk patent must be delivered at a temperature less than ambient temperature and higher than the freezing point of water. The cooling agents suitable and contemplated for use in the present invention do not have any such temperature requirements. Also, the cooling mixtures of the Rizk patent achieve their cooling effect through  
30 the latent heat of transformation, or evaporation, of both the dimethyl ether and the water components. The cooling agents of the present invention, in contrast, stimulate the cold receptors of the nervous system, and, thus,

achieve a cooling effect that is not dependent upon the temperature of the cooling agent relative to ambient temperature.

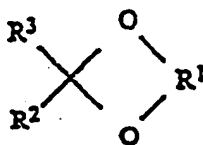
Cooling agents that may be used in the present invention include menthol, and the alkyl-substituted methanols disclosed in U.S. Patent No. 4,069,345 to Gascoyne et al. The cooling agent may also be acyclic sulphones or acyclic sulfoxides, phosphine oxides, alkyl-substituted alicyclic carboxylic acids, esters and amides, cyclohexan-amides, cyclic and acyclic amides, substituted ureas and sulphonamides. Examples of the foregoing are disclosed in U.S. Patent Nos. 4,318,900; 4,296,093; 4,136,164; 4,070,496; and 4,070,449 to Rowsell et al. Further, the cooling agent may also be N-hetero substituted-p-menthane-3-carboxamides as disclosed in U.S. Patent No. 4,190,643 to Watson et al. Still further, the cooling agent may be monomenthyl succinates, alkali metal salts of monomenthyl succinate, alkaline earth metal salts of monomenthyl succinate, and mixtures thereof. Examples of the foregoing are disclosed in U.S. Patent Nos. 5,725,865 and 5,843,466 to Mane et al. Yet further, the cooling agent can be an asymmetric carbonate, thiocarbonate or urethate as disclosed in U.S. Patent No. 5,703,123 to Pelzer et al. The cooling agent can also be a 2-(2-alkoxy-1-methylethyl)-5-methyl cyclohexanol derivative as disclosed in U.S. Patent No. 5,756,857 to Kuribayashi et al. Each patent cited in this paragraph is incorporated herein by reference.

When the cooling agent is a ketal, such as menthone glycerin acetal and the ketals disclosed in U.S. Patent No. 5,266,692 to Grub et al., which is incorporated herein by reference, the onset and duration of the effect of the cooling agent may be affected by manipulating the substituents on the ketal.

When the cooling agent is menthol lactate, the topical cooling composition preferably comprises an alkali metal carbonate and/or bicarbonate and/or alkaline earth metal carbonate as set forth in U.S.

Patent No. 5,783,725 to Kuhn et al., which is also incorporated herein by reference, to improve stability of the topical cooling composition.

It is believed that when the cooling composition comprises two or  
 5 more of the cooling agents, the cooling effect achieved by the cooling composition is enhanced. For example, U.S. Patent No. 5,451,404 to Furman discloses cooling compositions that are suitable for use in practicing the present invention. One example of a topical cooling composition of the Furman '404 patent comprises an effective amount of a  
 10 first cooling component that is a ketal of the formula



15

in which R<sup>1</sup> represents a C<sub>2</sub>-C<sub>6</sub>-alkylene radical having at least 1, but not more than 3, hydroxyl group(s) and either R<sup>2</sup> and R<sup>3</sup> independently of one another represent C<sub>1</sub>-C<sub>10</sub>-alkyl which is optionally substituted by 1 to 3 radicals selected from the group comprising hydroxyl, amino and halogen,  
 20 or C<sub>5</sub>-C<sub>7</sub>-cycloalkyl, or C<sub>6</sub>-C<sub>12</sub>-aryl, with the proviso that the total of the C atoms of R<sub>2</sub> and R<sub>3</sub> is not less than 3, or R<sub>2</sub> and R<sub>3</sub> together represent an alkylene radical which, together with the carbon atom which carries the radicals R<sup>2</sup> and R<sup>3</sup>, forms a 5-7-membered ring, and a second coolant component selected from the group consisting of menthol, carboxamides  
 25 and mixtures thereof.

The preferred cooling agents for the present invention include menthol, menthone glycerin acetal (a non-limiting example of the foregoing is available from Haarmann & Reimer GmbH under the trademark  
 30 FRESCOLAT<sup>®</sup> MGA), menthyl lactate (a non-limiting example of the foregoing is available from Haarmann & Reimer GmbH under the trademark FRESCOLAT<sup>®</sup> ML), menthyl pyrrolidane carboxylic acid (PCA)

(a non-limiting example of the foregoing is available from Quest International under the tradename QUESTICE L), N-2,3,-Trimethyl-2-isopropyl butanamide (a non-limiting example of the foregoing is available from ChiRex, Inc. under the tradename WS-23), N-ethyl-p-menthan-3-carboxamide (a non-limiting example is available from ChiRex, Inc. under the tradename WS-3), 3-1-methoxypropane-1,2-diol, (1-(2-hydroxyphenyl)4-(3-nitrophenyl)-1,2,3,6-tetrahydropyrimidine-2-one), C<sub>1</sub> to C<sub>5</sub> derivatives of 2-(2-alkoxy-1-methylethyl)-5-methyl cyclohexanols, 1-menthanyl carbonates and mixtures of the foregoing. Menthone glycerin acetal is the most preferred cooling agent. One reason why menthyl pyrrolidane carboxylic acid is a preferred cooling agent is because it exhibits moisturizing properties as well as coolant properties.

The cooling composition of the present invention comprises from about 0.01 wt% to about 10 wt% of the cooling agent, preferably from about 0.01 wt% to about 5 wt%, more preferably from about 0.1 wt% to about 2 wt%, even more preferably from about 0.1 wt% to about 1 wt%, and most preferably from about 0.2 wt% to about 0.8 wt%.

As stated above, the cooling composition is preferably a stick, spray or towelette. It is preferred that the cooling composition is a water-based system. In addition, it is preferred that the when the cooling composition is a water-based composition, the cooling composition further comprises an alcohol, such as ethanol, isopropyl alcohol and propanol. Alcohols act as a solvent and also exert a cooling effect that enhances the benefits of the present invention. When the cooling composition is a water-based system, it is preferred that the cooling composition comprises from about 5 wt% to about 15 wt% of an alcohol. The remainder of the cooling composition may be water. When a water-based system is used, it is preferred that the cooling composition comprises from about 0.01 wt% to about 5 wt% of the cooling agent.

The cooling composition may also be an anhydrous system. In an anhydrous system comprising alcohol, such as ethanol, isopropyl alcohol or propanol, it is preferred that the alcohol comprises the majority of the cooling composition other than the cooling agent. In an anhydrous, alcohol-free system, such as a cosmetic stick, the composition is comprised of esters, waxes and/or oils in place of the water and alcohol. When the cooling composition is an anhydrous system, the cooling composition may comprise up to 10 wt% of the cooling agent. It is more preferred that the cooling composition comprises from about 0.1 wt% to about 1 wt% of the cooling agent.

The cooling composition, whether a water-based system or an anhydrous system, may further include ingredients such as sunscreens, odor masking agents, natural/botanical extracts, alpha-hydroxy acids, polyhydroxy alpha-hydroxy acids, alpha-keto acids, vitamins, antimycobacterial agents, analgesics, lipidic compounds, moisturizers or lubricants.

When the cooling composition contains a natural/botanical extract, it is preferred that the natural/botanical extract comprises a soy extract, a black cohosh extract, or a ginseng extract, or mixtures thereof. More preferably, the natural/botanical extract will be a mixture of all three of the foregoing extracts.

Since many women experience feelings of anxiety during hot flashes, it is believed that when the cooling composition comprises a fragrant component, which is preferably a natural extract, the alleviation of the discomfort associated with hot flashes is augmented. It is believed that the aromatherapeutic benefits of the fragrant component will provide a calming effect, and thus synergistically enhance the cooling composition's effect on relieving the discomfort, both emotional as well as physiological, associated with hot flashes.

The cooling composition may also include emulsifiers, thickeners and preservatives. Emulsifiers (solubilizers) that can be used in the cooling compositions of the present invention can be cationic, anionic, non-ionic, 5 amphoteric, zwitterionic, or combinations thereof. However, it is preferred that the emulsifier is a polysorbate emulsifier. Non-limiting examples of polysorbate emulsifiers are Polysorbate 20 and Polysorbate 80. Examples of thickeners that can be used are, xanthan gum, magnesium aluminum silicate (a non-limiting example of the foregoing is available under the 10 tradename Veegum), cellulosic thickeners, and polymeric thickeners, such as CARBOPOL, PEMULEN™ copolymers and acrylate copolymers. A non-limiting example of an acrylate copolymer that may be used in the present invention is an acrylate/C<sub>10</sub> to C<sub>30</sub> alkyl acrylate copolymer.

15 It is preferred that the cooling composition also includes a neutralizer to adjust pH. The preferred neutralizer is sodium hydroxide. The pH of the cooling composition should be adjusted according to the cooling agent used. For example, it is preferred that when the cooling agent comprises menthone glycerin acetal that the pH of the cooling composition is greater 20 than 7. In contrast, when the cooling agent comprises menthyl lactate, it is preferred that the pH of the cooling composition is less than 7.

It is preferred that the cooling composition of the present invention has a preservative. Suitable preservatives include disodium 25 EDTA, methyl paraben and benzyl alcohol. Other suitable preservatives include EDTA salts, EDTA fatty acid conjugates, alkanols, especially ethanol, isopropyl alcohol, benzyl alcohol, parabens, sorbates, phenoxyethanol, urea derivatives and isothiazolinone.

30 An example of a contemplated composition that would be suitable for practicing the present invention is as follows:

EXAMPLE 1

	<u>INGREDIENT</u>	<u>Wt Percent of Total</u>
	<u>Composition</u>	
	Menthone glycerin acetal	0.01 to 5
5	Vehicle	
	Polysorbates	0.01 to 5
	Methylparaben	0.01 to 5
	Acrylates copolymer	0.01 to 4
	Sodium Hydroxide	0.01 to 2
10	Alcohol	5 to 15
	Disodium EDTA	0.01 to 0.8
	Water	QS

15 The cooling composition of the present invention described above is  
 used to alleviate the physical symptoms experienced by a woman during a  
 hot flash. It is contemplated that when the cooling composition may be  
 applied immediately when the woman either senses a hot flash about to  
 occur or after a hot flash begins. Although a woman may apply the cooling  
 composition to any surface area of her body that requires relief, it is  
 20 contemplated that the most useful areas for application will be the chest,  
 face and neck areas, particularly the areas around the temple and at the  
 base of the neck adjacent the spine. In addition, it is also believed that  
 topically applying the cooling composition to the wrist and arm areas will be  
 particularly useful in alleviating discomfort associated with a hot flash.

25 Although it is contemplated that the method of the present invention  
 will be used most often to alleviate the discomfort of a hot flash on an as  
 needed basis, it is believed that the method of the present invention may  
 be extended to prophylaxis. For example, many women have their slumber  
 30 disturbed by "night time" hot flashes. As stated above, the onset and  
 duration of action of the cooling agent may be manipulated via changes in  
 chemical structure. Accordingly, women who frequently experience such

night time hot flashes may apply, just prior to sleep, topical cooling compositions having cooling agents with either delayed onset or prolonged effect.

- 5           When the topical cooling composition is a spray (hereinafter "cooling spray"), it is believed that the optimum benefits of the present invention are achieved in the following manner. The user will spray the cooling spray onto the palm(s) of the hand(s) or onto the fingertips. The user will then transfer the cooling spray onto the skin. In order to avoid inhalation of the
- 10   cooling composition and to avoid contact of the cooling composition with the eyes, it is recommended that the cooling composition should never be directly sprayed onto or near the face area. When the topical cooling composition is a stick, towelette, lotion, cream or gel, (hereinafter collectively referred to as "non-spray cooling composition(s)"), the
- 15   consumer may also manually apply the non-spray cooling composition to the area of skin that feels uncomfortably warm or hot due to the hot flash. It is preferred that the non-spray cooling composition is spread over the surface of the skin, but not rubbed deeply into the skin. Extensive rubbing of the skin may intensify the feeling of heat experienced by the consumer,
- 20   and is preferably to be avoided.

#### EXAMPLE 2

- 25           A study was conducted to test the effectiveness of the present invention in alleviating discomfort and symptoms experienced by women during a hot flash.

- 30           Forty-five women between 40 and 60 years of age participated in the study. The participants experienced at least three to four hot flashes per day. Some participants experienced as many as ten hot flashes per day. In addition to hot flashes, the participants also reported experiencing



headaches, sleeplessness, mood changes, night sweats and/or erratic or stopped menstrual periods.

The participants were given spray bottles containing Sample A.

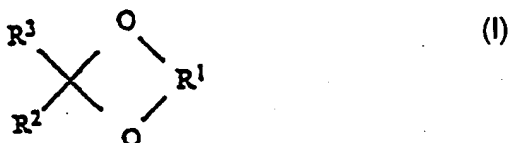
- 5 Sample A comprised 0.65 wt% menthone glycerin acetal in a compatible vehicle made according to Example 1 above. During a two-week period, the participants applied Sample A to various parts of their body when experiencing a hot flash. Those parts of the body to which the participants applied Sample A included the face, chest, neck/throat, shoulders, back,  
10 stomach, legs, arms, wrists and hands.

- Over sixty percent of the participants expressed that Sample A was effective in alleviating discomfort experienced during hot flash episodes. In addition, over sixty percent of the participants expressed that Sample A  
15 either met or exceeded their expectations of performance.

- Various modifications and alterations to the present invention may be appreciated based on a review of this disclosure. These changes and additions are intended to be within the scope and spirit of the present  
20 invention as defined by the following claims.

## WHEREFORE IT IS CLAIMED

1. A method of treating a hot flash, the method comprising the step of:
    - 5 applying topically a cooling composition having an effective amount of a cooling agent, wherein the cooling agent is substantially at ambient temperature when applied.
  2. The method of claim 1, wherein the cooling agent is selected
    - 10 from the group consisting of menthol, menthyl lactate, menthyl pyrrolidane carboxylic acid, N,2,3-trimethyl-2-isopropyl butanamide, N-ethyl-p-menthan-3-carboxamide, 3-1-menthoxy propane-1,2-diol, 1-(2-hydroxyphenyl)-4-(3-nitrophenyl)-1,2,3,6-tetrahydropyridine-2-one, 2-(2-alkoxy-1-methylethyl)-5-methyl cyclohexanols, 1-menthanyl carbonates, a
      - 15 formula (I) ketal, and mixtures thereof,
- wherein the formula (I) ketal is as follows:



- 20 in which R<sup>1</sup> represents a C<sub>2</sub>-C<sub>6</sub>-alkylene radical having at least 1, but not more than 3, hydroxyl group(s) and either R<sup>2</sup> and R<sup>3</sup> independently of one another represent C<sub>1</sub>-C<sub>10</sub>-alkyl which is optionally substituted by 1 to 3
- 25 radicals selected from the group comprising hydroxyl, amino and halogen, or C<sub>5</sub>-C<sub>7</sub>-cycloalkyl, or C<sub>6</sub>-C<sub>12</sub>-aryl, with the proviso that the total of the C atoms of R<sub>2</sub> and R<sub>3</sub> is not less than 3, or R<sub>2</sub> and R<sub>3</sub> together represent an alkylene radical which, together with the carbon atom which carries the radicals R<sup>2</sup> and R<sup>3</sup>, forms a 5-7-membered ring.

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3. The method of claim 1, wherein the cooling agent is selected from the group consisting of menthyl pyrrolidane carboxylic acid, menthone glycerin acetal, menthyl lactate, and mixtures thereof.

5 4. The method of claim 1, wherein the cooling agent comprises menthone glycerin acetal.

5. The method of claim 1, wherein the cooling agent comprises menthyl pyrrolidane carboxylic acid.

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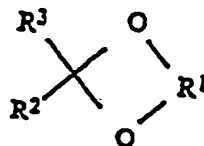
6. The method of claim 1, wherein the cooling agent comprises from about 0.01 wt% to about 5 wt% of menthone glycerin acetal.

7. The method of claim 3, wherein the cooling agent comprises menthyl pyrrolidane carboxylic acid and menthone glycerin acetal.

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8. The method of claim 1, wherein the cooling agent comprises: an effective amount of a first cooling component that is a ketal of the formula

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in which R<sup>1</sup> represents a C<sub>2</sub>-C<sub>6</sub>-alkylene radical having at least 1, but not more than 3, hydroxyl group(s) and either R<sup>2</sup> and R<sup>3</sup> independently of one another represent C<sub>1</sub>-C<sub>10</sub>-alkyl which is optionally substituted by 1 to 3 radicals selected from the group comprising hydroxyl, amino and halogen, or C<sub>5</sub>-C<sub>7</sub>-cycloalkyl, or C<sub>6</sub>-C<sub>12</sub>-aryl, with the proviso that the total of the C atoms of R<sub>2</sub> and R<sub>3</sub> is not less than 3, or R<sub>2</sub> and R<sub>3</sub> together represent an

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alkylene radical which, together with the carbon atom which carries the radicals  $R^2$  and  $R^3$ , forms a 5-7-membered ring, and

5 a second cooling component selected from the group consisting of menthol, carboxamides, and mixtures thereof.

9. The method of claim 8, wherein the first cooling component is menthone glycerin acetal, and wherein said carboxamides is selected from the group consisting of N,2,3-trimethyl-2-isopropyl butanamide, N-ethyl-p-  
10 menthan-3-carboxamide, and a mixture thereof.

10. The method of claim 1, wherein the cooling composition is applied to a part of the body selected from the group consisting of the face, neck, chest, wrist, arm, and combinations thereof.

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11. The method of claim 10, wherein the cooling composition is applied to a temple area of the face.

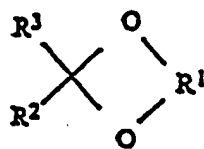
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12. The method of claim 5, further comprising moisturizing skin.

13. A method of providing prolonged cooling relief from the feeling of heat associated with a hot flash, comprising applying topically a cooling composition having an effective amount of a cooling agent selected from the group consisting of menthol, menthyl lactate, menthyl pyrrolidane  
25 carboxylic acid, N,2,3-trimethyl-2-isopropyl butanamide, N-ethyl-p-menthan-3-carboxamide, 3-1-menthoxy propane-1,2-diol, 1-(2-hydroxyphenyl)-4-(3-nitrophenyl)-1,2,3,6-tetrahydropyridine-2-one, 2-(2-alkoxy-1-methylethyl)-5-methyl cyclohexanols, 1-menthanyl carbonates, a formula (I) ketal, and mixtures thereof,

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wherein the formula (I) ketal is as follows:



(I)

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in which  $R^1$  represents a  $C_2$ - $C_6$ -alkylene radical having at least 1, but not more than 3, hydroxyl group(s) and either  $R^2$  and  $R^3$  independently of one another represent  $C_1$ - $C_{10}$ -alkyl which is optionally substituted by 1 to 3 radicals selected from the group comprising hydroxyl, amino and halogen, or  $C_5$ - $C_7$ -cycloalkyl, or  $C_6$ - $C_{12}$ -aryl, with the proviso that the total of the C atoms of  $R_2$  and  $R_3$  is not less than 3, or  $R_2$  and  $R_3$  together represent an alkylene radical which, together with the carbon atom which carries the radicals  $R^2$  and  $R^3$ , forms a 5-7-membered ring.

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14. A method of alleviating one or more physical symptoms experienced in connection with a hot flash, comprising applying topically a composition having an effective amount of a cooling agent, wherein the cooling agent is substantially at ambient temperature when applied.

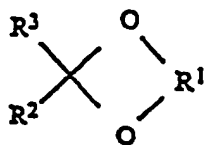
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15. The method of claim 14, wherein said cooling agent is selected from the group consisting of menthol, menthyl lactate, menthyl pyrrolidane carboxylic acid, N,2,3-trimethyl-2-isopropyl butanamide, N-ethyl-p-menthan-3-carboxamide, 3-1-menthoxy propane-1,2-diol, 1-(2-hydroxyphenyl)-4-(3-nitrophenyl)-1,2,3,6-tetrahydropyridine-2-one, 2-(2-alkoxy-1-methylethyl)-5-methyl cyclohexanols, 1-menthanyl carbonates, a

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formula (I) ketal, and mixtures thereof,

wherein the formula (I) ketal is as follows:



(I)

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in which R<sup>1</sup> represents a C<sub>2</sub>-C<sub>6</sub>-alkylene radical having at least 1, but not more than 3, hydroxyl group(s) and either R<sup>2</sup> and R<sup>3</sup> independently of one another represent C<sub>1</sub>-C<sub>10</sub>-alkyl which is optionally substituted by 1 to 3 radicals selected from the group comprising hydroxyl, amino and halogen, or C<sub>5</sub>-C<sub>7</sub>-cycloalkyl, or C<sub>6</sub>-C<sub>12</sub>-aryl, with the proviso that the total of the C atoms of R<sub>2</sub> and R<sub>3</sub> is not less than 3, or R<sub>2</sub> and R<sub>3</sub> together represent an alkylene radical which, together with the carbon atom which carries the radicals R<sup>2</sup> and R<sup>3</sup>, forms a 5-7-membered ring.

10           16.    The method of claim 14, wherein said physical symptom is selected from the group consisting of anxiety, a sense of unease, pressure in the hand, tingling sensations, sweating, faintness, dizziness, nausea, breathlessness, sensations of body heat, and combinations thereof.

15           17.    The method of claim 15, wherein said physical symptom is selected from the group consisting of sweating, anxiety, a sense of unease, sensations of internal body heat, dizziness and combination thereof.

20           18.    The method of claim 14, wherein said cooling agent is selected from the group consisting of menthyl pyrrolidane carboxylic acid, menthone glycerin acetal, menthyl lactate, and mixtures thereof.

25           19.    The method of claim 14, wherein the cooling composition is applied to a part of the body selected from the group consisting of the face, neck, chest, wrist, arm, and combinations thereof.

20           20.    The method of claim 14, wherein the cooling composition is applied to a temple area of the face.

30           21.    A method of providing relief from internal body heat associated with a hot flash, the method comprising applying topically a

cooling composition having an effective amount of a cooling agent, wherein the cooling agent is substantially at ambient temperature when applied.

22. The method of claim 21, wherein perspiration accompanies the internal body heat.

23. The method of claim 21, wherein said cooling agent is selected from the group consisting of menthol, menthyl lactate, menthyl pyrrolidane carboxylic acid, N,2,3-trimethyl-2-isopropyl butanamide, N-ethyl-p-menthan-3-carboxamide, 3-1-menthoxy propane-1,2-diol, 1-(2-hydroxyphenyl)-4-(3-nitrophenyl)-1,2,3,6-tetrahydropyridine-2-one, 2-(2-alkoxy-1-methylethyl)-5-methyl cyclohexanols, 1-menthanyl carbonates, a formula (I) ketal, and mixtures thereof, wherein the formula (I) ketal is as follows:



in which R<sup>1</sup> represents a C<sub>2</sub>-C<sub>6</sub>-alkylene radical having at least 1, but not more than 3, hydroxyl group(s) and either R<sup>2</sup> and R<sup>3</sup> independently of one another represent C<sub>1</sub>-C<sub>10</sub>-alkyl which is optionally substituted by 1 to 3 radicals selected from the group comprising hydroxyl, amino and halogen, or C<sub>5</sub>-C<sub>7</sub>-cycloalkyl, or C<sub>6</sub>-C<sub>12</sub>-aryl, with the proviso that the total of the C atoms of R<sub>2</sub> and R<sub>3</sub> is not less than 3, or R<sub>2</sub> and R<sub>3</sub> together represent an alkylene radical which, together with the carbon atom which carries the radicals R<sup>2</sup> and R<sup>3</sup>, forms a 5-7-membered ring.

24. The method of claim 23, wherein said cooling agent is selected from the group consisting of menthyl pyrrolidane carboxylic acid, menthone glycerin acetal, menthyl lactate, and mixtures thereof.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/02638

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61K 31/40, 31/16, 31/015

US CL : 514/412, 613, 763

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/412, 613, 763; 424/45, 47, 65

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, CAPLUS.

search term: hot and (flush or flash), menopausal, coolant or cooling, menthone or menthyl, pyrrolidone, lactate.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,917,613 A (HUMBERT et al.) 04 November 1975, col. 1-2.	1-24
Y	US 4,230,688 A (ROWSELL et al.) 28 October 1980, col. 1, lines 27-34; col. 7, lines 46-63.	1-24
Y	US 5,451,404 A (FURMAN) 19 September 1995, col. 7, lines 19-31; col. 9, lines 8-24.	1-24
Y	US 5,730,957 A (RIZK) 24 March 1998, col. 1, lines 56-58.	1-24

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A*	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

17 APRIL 2000

Date of mailing of the international search report

13 JUN 2000

 Name and mailing address of the ISA/US  
 Commissioner of Patents and Trademarks  
 Box PCT  
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

  
 Shengjun Wang

Telephone No. (703) 308-1235



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/02638

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database Medline on STN, US National Library of Medicine, (Bethesda, MD, USA), No. 80054117, STURDEE, D.W. et al. 'Thermography of menopausal hot flushes,' abstract, Maturitas, Febraury 1979, Vol. 1, No. 3, pages 201-205.	1-24